

HYPOTHESIS

Spongiuous therapy of iron overload with hipcidin overexpressed macrophages

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Iron overload is a major cause of morbidity and mortality in some diseases such as beta thalassemia. Conventional therapies with phlebotomy and iron chelating agents have shown no profound effect on iron excessive disease. Moreover, hepcidin as an iron transport inhibitor can absorb more iron than normal level following overexpression in macrophages. For this purpose, We hypothesised that repeat transplantation of manipulated macrophages and their replacement, can remove the excess iron and decrease iron toxicity, a process that is called, spongiuous therapy.

Keywords: Iron Overload; Thalassemia; Iron Chelating Agents; Macrophages; Transplantation; Hepcidin

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Introduction

Iron is a bio-metal agent that is essential for many biological processes [1, 2]. Because of its ability to oxidation and reduction readily by switching between ferric (Fe³⁺) and ferrous (Fe²⁺) states, iron is a key component of many proteins such as hemoglobin, myoglobin and mitochondrial electron transport chain enzymes [1, 2]. Following absorption, iron combines with iron transporting protein, called transferrin, and then enters the intracellular pool, mostly as a ferritin form in macrophages of the reticuloendothelial system and/or a complex with hemoglobin in red blood cells [1]. There is no excretory mechanism for iron, and its level is only controlled via absorption [3, 4]. Therefore, iron can be easily

accumulated following conditions that induce iron storage [3, 5].

Iron overload means the accumulation of excess iron in the body due to primary and secondary causes [6]. The well-known example of primary iron overload is the hereditary hemochromatosis in which the intestinal iron absorption is increased [3]. Thalassemia major, sideroblastic anemia and chronic liver diseases represent the common causes of secondary iron overload [3]. As iron overload has toxic effects, it can promote diabetes, cardiomyopathy, hepatocellular carcinoma, arthritis, hypogonadism, cirrhosis, osteoporosis and fractures [7-9].

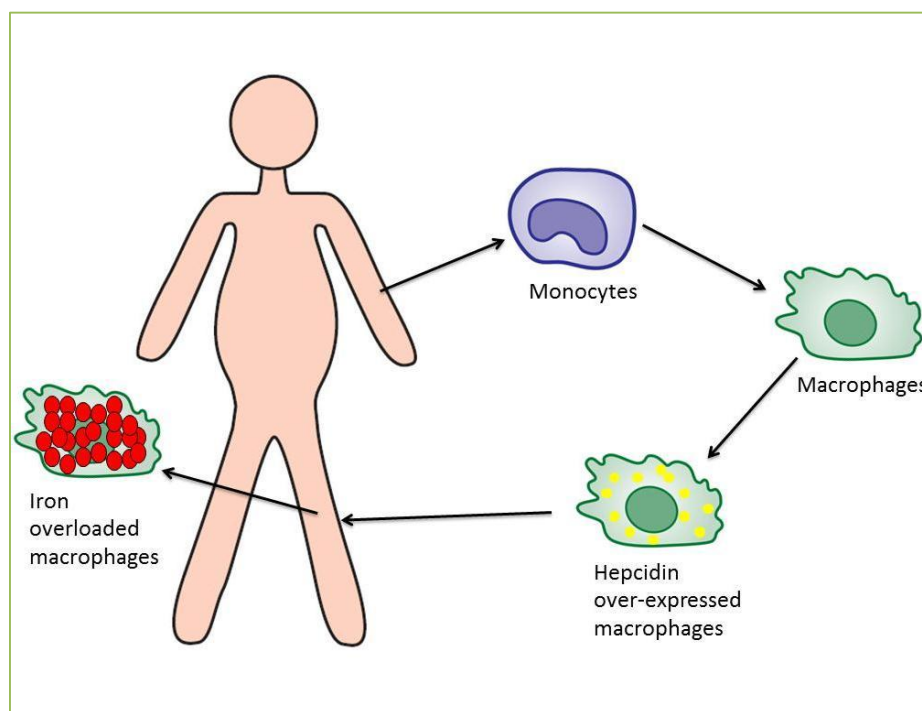


Figure 1. Schematic representation of the hypothesis design. Briefly, the patient monocytes are differentiated to the macrophages and infused into the medullary cavity of the femur and tibia (spongius therapy) followed by hepcidin overexpression and finally, refreshed by the novel (unloaded) manipulated cells.

Iron overload can be treated with phlebotomy and iron chelators [9]. But in severe conditions such as thalassemia, these therapies cannot prevent iron overload complications. For this reason, it is also the major cause of morbidity and mortality in patients with beta thalassemia [9, 10].

Hypothesis

We hypothesized that the excessive iron would be absorbed by engrafting the manipulated macrophages into the bone marrow cavity. Following leukocyte collection from peripheral blood of patients by leukopheresis, monocytes are easily separated from the other leukocytes by density gradient centrifugation using Nycoprep 1.068. Then, in the presence of the human serum for 7-10 days, the monocytes are differentiated to the macrophages [11]. It has been already found that the hepcidin hormone inhibits iron transport out of macrophages by inducing ferroportin internalization and degradation [12, 13]. So, upon overexpression of hepcidin in macrophages, these manipulated cells are able to absorb iron greater than normal level. Finally, these cells can be infused into the medullary cavity of the femur and tibia (spongius therapy) and refreshed by the novel (unloaded) cells following overloading with Iron.

Evaluation of the hypothesis

There are different methods to evaluate the iron status of the body. The easiest and most straightforward technique is the evaluation of the blood iron level. Total iron binding capacity (TIBC), transferrin iron saturation, free unbound iron and specially ferritin are the most important serum iron indexes. Moreover, tissue storage of iron can be calculated by the Perls' Prussian blue staining of the bone marrow aspirate. Long-term follow-up after spongius therapy can be achieved by the survival rate of chronically transfused patients. Refreshing time for overloaded macrophage depends on the iron rate of the target bone marrow and in vivo longevity of these cells.

Discussion

This hypothesis shows several strong points, if be confirmed. 1) The graft can be easily achieved by the phlebotomy method without any aggressive intention. 2) Autologous transplantation will hinder the adverse immunologic reactions. 3) The natural body mechanisms and materials are employed to differentiation of the monocytes into the macrophages. 4) Because of lack of the lymph vessel in the bone cavity, the macrophages cannot leave this tissue and diffuse to the other organs. This leads to the accumulation of macrophages in the distinct area and allows them to be exchangeable. 5) On the other hand, due to the existence of

blood vessel in bone cavity, the transplanted cells have access to the blood nutrients, oxygen and especially iron.

Manipulation of macrophages allows removing more iron than normal. Although the natural mechanisms are involved in this process, concern of cancer development may arise because of the manipulation and distance away from their native niche. However, the long-term in vivo and in vitro study should be proposed to assess the transformation and malignancy potency of manipulated cells.

We adopted "spongy therapy" terminology, because the macrophages absorb the body excess iron and then these cells are periodically exchanged with the new ones, like sponge. Besides iron overload therapy, spongy therapy can be used for treatment of the diseases associated with the excessive substances such as the lipidemia and gamma globulinemia. However, the autologous macrophages can remove the excess element and then are exchanged without any unwanted side effects.

Conclusions

Because of absorbent properties of manipulated macrophages, spongy therapy can be used for treatment of iron overload. It is expected that this therapy will decrease the iron storage of the patients with the overloaded iron, and increase their survival rate.

Conflicting interests

The authors have declared that no competing interests exist.

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